

MAR 17 2009

Attorney Docket No. P67564US1
Application No. 10/501,814Amendments to the claims:

This listing of claims replaces all prior versions, and listings, of claims in the application.

Listing of claims:

1 (currently amended): A method of diagnosing or prognostication a neurodegenerative Alzheimer's disease in a subject, or determining whether a subject is at increased risk of developing said disease, comprising:

determining a level and/or an activity of

(i) a transcription product of the gene coding for the voltage-gated ion channel sodium channel type 2A (SCN2A)[,] and/or

(ii) a translation product of the gene coding for the voltage-gated ion channel SCN2A in a sample from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby diagnosing or prognosticating said neurodegenerative Alzheimer's disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

2 (currently amended): A method of monitoring the progression of a neurodegenerative Alzheimer's disease in a subject, comprising:

Attorney Docket No. P67564US1
Application No. 10/501,814

determining a level and/or an activity of

- (i) a transcription product of the gene coding for the voltage-gated ion channel SCN2A[,] and/or
- (ii) a translation product of the gene coding for the voltage-gated ion channel SCN2A[.]

in a sample from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby monitoring the progression of said neurodegenerative Alzheimer's disease in said subject.

Claims 3 and 4 (cancelled).

5 (previously presented): The method according to claim 1 wherein said sample comprises a cell, or a tissue, or a body fluid, in particular cerebrospinal fluid or blood.

6 (currently amended): The method according to claim 1 wherein said reference value is that of a level and/or an activity of

- (i) a transcription product of the gene coding for the voltage-gated ion channel SCN2A[,] and/or
- (ii) a translation product of the gene coding for the voltage-gated ion channel SCN2A[.]

in a sample from a subject not suffering from said neurodegenerative Alzheimer's disease.

7 (previously presented): The method according to claim 1 wherein an alteration in the level and/or activity of a transcription product of the gene coding for the voltage-gated ion channel SCN2A

Attorney Docket No. P67564US1
Application No. 10/501,814

and/or a translation product of the gene coding for voltage-gated ion channel SCN2A, in a sample cell, or tissue, or body fluid, in particular cerebrospinal fluid, from said subject relative to a reference value representing a known health status indicates a diagnosis of Alzheimer's disease in said subject.

8 (currently amended): The method according to any of claim 1, further comprising comparing a level and/or an activity of

- (i) a transcription product of the gene coding for the voltage-gated ion channel SCN2A[,] and/or
 - (ii) a translation product of the gene coding for the voltage-gated ion channel SCN2A[,]
- in a series of samples taken from said subject over a period of time.

9 (original): The method according to claim 8 wherein said subject receives a treatment prior to one or more of said sample gatherings.

10 (original): The method according to claim 9 wherein said level and/or activity is determined before and after said treatment of said subject.

11 (currently amended): A kit for diagnosing Alzheimer's disease in a subject, said kit comprising:

- (a) at least one reagent which is selected from the group consisting of
 - (i) reagents that selectively detect a transcription product of the gene coding for the voltage-gated ion channel SCN2A, and

Attorney Docket No. P67564US1
Application No. 10/501,814

- (ii) reagents that selectively detect a translation product of the gene coding for the voltage-gated ion channel SCN2A, and
- (b) an instruction for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease by
 - (i) detecting a level, or an activity, or both said level and said activity, of said transcription product and/or said translation product of the gene coding for the voltage-gated ion channel SCN2A in a sample from said subject; and
 - (ii) diagnosing Alzheimer's disease,

wherein a varied level, or activity, or both said level and said activity, of said transcription product and/or said translation product compared to a reference value representing a known health status; or a level, or activity, or both said level and said activity, of said transcription product and/or said translation product similar or equal to a reference value representing a known disease status indicates a diagnosis of Alzheimer's disease.

12 (currently amended): A method of treating Alzheimer's disease in a subject comprising administering to said subject in a therapeutically or prophylactically effective amount an agent or agents which directly or indirectly affect an activity and/or a level of (i) the gene coding for the voltage-gated ion channel SCN2A, and/or (ii) a transcription product of the gene coding for the voltage-gated ion channel SCN2A, and/or (iii) a translation product of the gene coding for the voltage-gated ion channel SCN2A[.].

Attorney Docket No. P67564US1
Application No. 10/501,814

13 (previously presented): A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of (i) the gene coding for the voltage-gated ion channel SCN2A and/or (ii) a transcription product of the gene coding for the voltage-gated ion channel SCN2A and/or (iii) a translation product of the gene coding for the voltage-gated ion channel SCN2A.

14 (previously presented): A pharmaceutical composition comprising a modulator according to claim 13 in combination with a pharmaceutically acceptable carrier or diluent.

15 (previously presented): A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of (i) the gene coding for the voltage-gated ion channel SCN2A, and/or (ii) a transcription product of the gene coding for the voltage-gated ion channel SCN2A, and/or (iii) a translation product of the gene coding for the voltage-gated ion channel SCN2A and/or (iv) a fragment, or derivative, or variant of (i) to (iii) for use in a pharmaceutical composition.

16 (previously presented): Use of a modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of (i) the gene coding for the voltage-gated ion channel SCN2A, and/or (ii) a transcription product of the gene coding for the voltage-gated ion

Attorney Docket No. P67564US1
Application No. 10/501,814

channel SCN2A, and/or (iii) a translation product of the gene coding for the voltage-gated ion channel SCN2A or a preparation of a medicament for treating Alzheimer's disease.

17 (previously presented): A kit, comprising in one or more containers, a therapeutically effective amount of the pharmaceutical composition of claim 14.

18 (previously presented): A recombinant, non-human animal comprising a non-native gene sequence coding for the voltage-gated ion channel SCN2A, said animal being obtainable by:

- (i) providing a gene targeting construct comprising said gene sequence and a selectable marker sequence, and
- (ii) introducing said targeting construct into a stem cell of a non-human animal, and
- (iii) introducing said non-human animal stem cell into a non-human embryo, and
- (iv) transplanting said embryo into a pseudopregnant non-human animal, and
- (v) allowing said embryo to develop to term, and
- (vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and
- (vii) breeding the genetically altered non-human animal of step (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said disruption results in said non-human animal exhibiting a predisposition to developing symptoms of Alzheimer's disease.

Attorney Docket No. P67564US1
Application No. 10/501,814

19 (previously presented): Use of the recombinant, non-human animal according to claim 18 for screening, testing, and validating compounds, agents, and modulators in the development of diagnostics and therapeutics to treat Alzheimer's disease.

20 (currently amended): An assay for screening for a modulator of one or more substances selected from the group consisting of

- (i) the gene coding for the voltage-gated ion channel SCN2A, and/or
- (ii) a transcription product of the gene coding for the voltage-gated ion channel SCN2A, and/or
- (iii) a translation product of the gene coding for the voltage-gated ion channel SCN2A,

said method comprising:

- (a) contacting a cell with a test compound;
- (b) measuring the activity and/or level of one or more substances recited in (i) to (iv) (iii);
- (c) measuring the activity and/or level of one or more substances recited in (i) to (iv) (iii) in a control cell not contacted with said test compound; and
- (d) comparing the levels and/or activities of the substance in the cells of step (b) and (c), wherein an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of said diseases or disorders Alzheimer's disease.

Attorney Docket No. P67564US1
Application No. 10/501,814

21 (currently amended): A method of screening for a modulator of Alzheimer's disease of one or more substances selected from the group consisting of

- (i) the gene coding for the voltage-gated ion channel SCN2A, and/or
- (ii) a transcription product of the gene coding for the voltage-gated ion channel SCN2A, and/or
- (iii) a translation product of the gene coding for the voltage-gated ion channel SCN2A,

said method comprising:

- (a) administering a test compound to a test animal which is predisposed to developing or has already developed symptoms of Alzheimer's disease in respect of the substances recited in (i) to (iii);
- (b) measuring the activity and/or level of one or more substances recited in (iii);
- (c) measuring the activity and/or level of one or more substances recited in (i) in a matched control animal which is predisposed to developing or has already developed symptoms of a neurodegenerative Alzheimer's disease or related diseases or disorders in respect to the substances recited in (i) to (iii) and to which animal no such test compound has been administered;
- (d) comparing the activity and/or level of the substance in the animals of step (b) and (c), wherein an alteration in the activity and/or level of substances in the test animal indicates that the test compound is a modulator of Alzheimer's disease.

Attorney Docket No. P67564US1
Application No. 10/501,814

22 (previously presented): The method according to claim 21 wherein said test animal and/or said control animal is a recombinant animal which expresses the voltage-gated ion channel SCN2A, under the control of a transcriptional control element which is not the native SCN2A gene transcriptional control element.

23 (currently amended): A method of testing a compound, preferably of screening a plurality of compounds, for inhibition of binding between a ligand and the voltage-gated ion channel SCN2A, said method comprising the steps of:

- (i) adding a liquid suspension of said voltage-gated ion channel SCN2A, to a plurality of containers;
- (ii) adding a compound, preferably a plurality of compounds, to be screened for said inhibition of binding to said plurality of containers;
- (iii) adding a detectable ligand, in particular a fluorescently detectable ligand, to said containers;
- (iv) incubating the liquid suspension of said voltage-gated ion channel SCN2A, and said compound, preferably said plurality of compounds, and said ligand;
- (v) measuring amounts of detectable ligand or fluorescence associated with said voltage-gated ion channel SCN2A; and
- (vi) determining the degree of inhibition by one or more of said compounds of binding of said ligand to said voltage-gated ion channel SCN2A, or said fragment.

Attorney Docket No. P67564US1
Application No. 10/501,814

24 (previously presented): A method of testing a compound, preferably of screening a plurality of compounds, to determine the degree of binding of said compound or compounds to the voltage-gated ion channel SCN2A, said method comprising the steps of:

- (i) adding a liquid suspension of said voltage-gated ion channel SCN2A, to a plurality of containers;
- (ii) adding a detectable compound, preferably a plurality of detectable compounds, in particular fluorescently detectable compounds, to be screened for said binding to said plurality of containers;
- (iii) incubating the liquid suspension of said voltage-gated ion channel SCN2A and said compound, preferably said plurality of compounds;
- (iv) measuring amounts of detectable compound or fluorescence associated with said voltage-gated ion channel SCN2A; and
- (v) determining the degree of binding by one or more of said compounds to said voltage-gated ion channel SCN2A.

25 (previously presented): A method for producing a medicament comprising the steps of (i) identifying a modulator of Alzheimer's disease by a method according to claim 20 and (ii) admixing the modulator with a pharmaceutical carrier.

Attorney Docket No. P67564US1
Application No. 10/501,814

26 (original): A method for producing a medicament comprising the steps of (i) identifying a compound as an inhibitor of binding between a ligand and the SCN2A gene product by a method according to claim 23 and (ii) admixing the compound with a pharmaceutical carrier.

27 (original): A method for producing a medicament comprising the steps of (i) identifying a compound as a binder to a SCN2A gene product by a method according to claim 24 and (ii) admixing the compound with a pharmaceutical carrier.

28 (previously presented): A medicament obtainable by the method according to claim 25.

29 (currently amended): A medicament obtained by the method according to claim 25 26.

30 (previously presented): A protein molecule, said protein molecule being a translation product of the gene coding for the voltage-gated ion channel SCN2A, for use as a diagnostic target for detecting Alzheimer's disease.

31 (currently amended): A protein molecule, said protein molecule being a translation product of the gene coding for the voltage-gated ion channel SCN2A, or a fragment, for use as a screening target for reagents or compounds preventing treating Alzheimer's disease.

Attorney Docket No. P67564US1
Application No. 10/501,814

32 (previously presented): Use of an antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of the gene coding for the voltage-gated ion channel SCN2A, for detecting the pathological state of a cell in a sample from a subject, comprising immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell.